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CKJ Review

CKJ REVIEW

The complex interplay between kidney injury and inflammation

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ABSTRACT

Acute kidney injury (AKI) has gained significant attention following patient safety alerts about the increased risk of harm to patients, including increased mortality and hospitalization. Common causes of AKI include hypovolaemia, nephrotoxic medications, ischaemia and acute glomerulonephritis, although in reality it may be undetermined or multifactorial. A period of inflammation either as a contributor to the kidney injury or resulting from the injury is almost universally seen. This article was compiled following a workshop exploring the interplay between injury and inflammation. AKI is characterized by some degree of renal cell death through either apoptosis or necrosis, together with a strong inflammatory response. Studies interrogating the resolution of renal inflammation identify a whole range of molecules that are upregulated and confirm that the kidneys are able to intrinsically regenerate after an episode of AKI, provided the threshold of damage is not too high. Kidneys are unable to generate new nephrons, and dysfunctional or repeated episodes will lead to further nephron loss that is ultimately associated with the development of renal fibrosis and chronic kidney disease (CKD). The AKI to CKD transition is a complex process mainly facilitated by maladaptive repair mechanisms. Early biomarkers mapping out this process would allow a personalized approach to identifying patients with AKI who are at high risk of developing fibrosis and subsequent CKD. This review article highlights this process and explains how laboratory models of renal inflammation and injury assist with understanding the underlying disease process and allow interrogation of medications aimed at targeting the mechanistic interplay.

Keywords: acute kidney injury, glomerulonephritis, inflammation, renal fibrosis

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INTRODUCTION

Over the past few years, acute kidney injury (AKI) has gained significant attention following patient safety alerts about the increased risks of harm to patients who experience an episode of AKI. It is estimated that one in five emergency admissions into hospital is associated with AKI [1] and that one in three patients in hospital with AKI develops it while in hospital [2]. AKI is responsible for prolonging inpatient care and contributing to ~100 000 deaths annually in the UK [3]. AKI is defined as a sudden alteration in the function of the kidney due to a variety of causes. It is typically reported in terms of measurable clinical outcomes, with an increase in the serum creatinine concentration and/or a reduction in the patient's urine output being the most universally recognized definition [4]. These measurable outcomes define whether a patient has clinical features of AKI and they have improved standardization across clinical settings and research studies. However, they tell us very little about the underlying cause or mechanisms that have led to the injury itself. The most common causes of AKI include hypovolaemia, nephrotoxic medications, ischaemia and acute glomerulonephritis, although in reality it may be undetermined or multifactorial [5, 6]. Within the mechanisms of AKI, one likely area of consistency is a period of inflammation either as a contributor or as a consequence of the renal injury, for example, systemic lupus erythematosus as an inflammatory disease causing glomerulonephritis or nephrotoxic kidney injury causing local renal inflammation, respectively. This article was compiled as a result of a multispecialty kidney injury and inflammation event attended by the authors. The aim of this review is to discuss the complex interplay between kidney injury and inflammation with regard to its mechanisms, diagnosis and potential targets for treatment. It also aims to consider future directions for further research to help improve our understanding of this disease process and improve the clinical outcomes of our patients.

CELLULAR AND MOLECULAR MECHANISMS OF INFLAMMATION IN RESPONSE TO RENAL INJURY

Understanding the cellular and molecular mechanisms that lead to renal inflammation is one of the most promising ways to identify early targets for treatment or prevention of AKI (Figure 1). Inflammation is a physiological process designed to protect the body against an acute injurious stimulus, such as ischaemia, toxins or pathogens. In a healthy individual, these stimuli are initially detected by the kidney through immune cells that include not only tissue-resident dendritic cells and macrophages, but also native renal cells that are able to express receptors for sensing damage (for excellent recent reviews on the interactions between kidneys and the immune system, the reader is directed to Ernandez *et al.* [7] and Tecklenborg *et al.* [8]). These intrarenal immune cells respond to such stimuli by actively secreting cytokines such as interleukin (IL)-1 and IL-6 and chemokines such as monocyte chemoattractant protein-1,

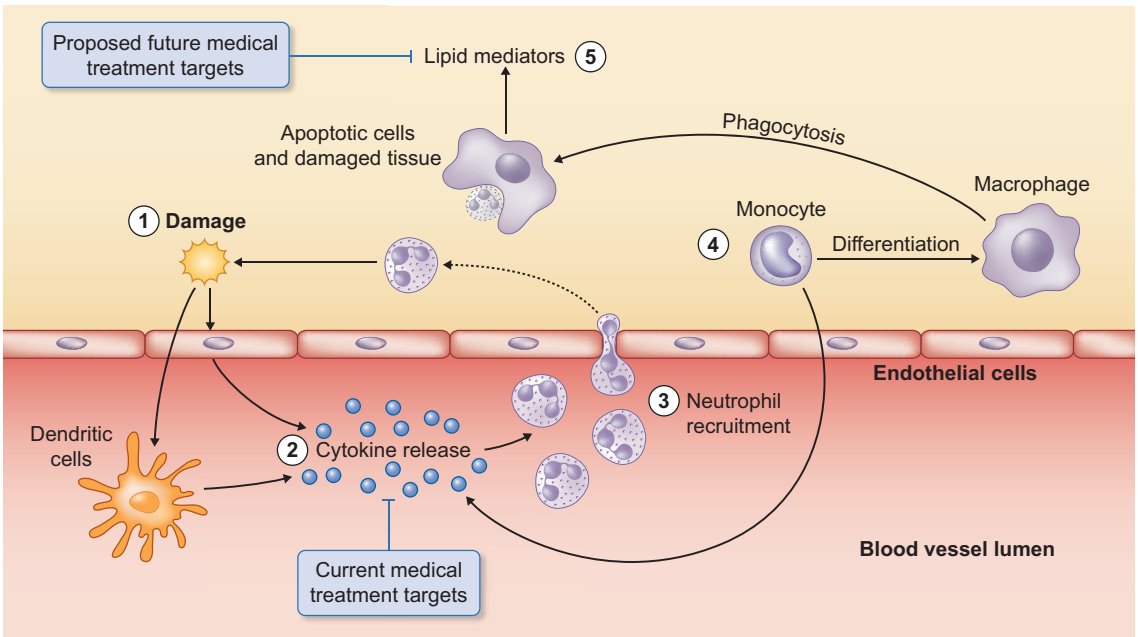

FIGURE 1: Cellular and molecular mechanisms of inflammation. Kidney damage is recognized by resident renal cells, dendritic cells and macrophages (as shown in area 1). Their response of cytokine and chemokine secretion is the current target for most treatments (area 2). Cytokine release triggers leucocyte recruitment to the side of damage beginning with the non-specific pathogen destruction of neutrophils (area 3). Monocytes are recruited to release further cytokine damage and differentiate into phagocytosing macrophages for the removal of apoptotic cells and damaged tissue to restore tissue homeostasis (area 4). Resolution of the damaged tissue is often accomplished by lipid mediators that could be the future targets for medical treatments of chronic inflammatory diseases.

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which migrate to nearby blood vessels and recruit leucocytes from the circulation to the area of damage to destroy invading pathogens, repair damaged tissue and restore tissue homeostasis [9].

The recruitment of leucocytes to the kidney occurs in a sequential manner to efficiently repair damage and restore renal function. Neutrophils are usually the first to be recruited to the area, as these cells are non-specific and are able to release their toxic granule contents to destroy invading pathogens at the site of inflammation [10]. However, as this is non-specific, these cells are also able to induce tissue damage and thus a second phase of monocytes is recruited from the bloodstream. These cells are more specific and can be subdivided into two groups: M1 and M2 monocytes. M1 monocytes release cytokines to destroy any pathogens that were not destroyed by the neutrophils. M2 monocytes differentiate into macrophages and phagocytose damaged tissue and apoptotic neutrophils to restore homeostasis to the tissue [11].

Studies interrogating the resolution of renal inflammation in acute inflammatory models identified a whole range of molecules that are increased in the tissue during the resolution phase of inflammation [12]. These molecules are most commonly lipid mediators that are released by neutrophils and monocytes at the site of inflammation, where they act to reduce the infiltration of neutrophils and promote the phagocytic clearance of apoptotic cells by macrophages [13]. Many *in vitro* and *in vivo* studies have been performed assessing the role of these lipid mediators in preventing or treating AKI. They have been shown to mitigate sepsis-associated AKI [14], improve tubular function after kidney ischaemia–reperfusion (KIR) injury [15] and blunt the development of lupus nephritis in lupus-prone New Zealand Black × New Zealand White (NZB/W) F1 mice[16].

AKI AND ITS PROGRESSION TO CHRONIC KIDNEY DISEASE (CKD)

Irrespective of the underlying cause, AKI is characterized by some degree of renal cell death through either apoptosis or necrosis and a strong inflammatory response [17, 18]. More recent studies have demonstrated evidence of necroptosis, ferroptosis, parthanatos and mitochondrial permeability transition-induced regulated necrosis [19]. These all represent different pathways leading to an inflammatory response and thus different targets for potential AKI therapeutic development. While epithelial cells of the proximal tubule are mostly affected in the main causes of AKI, there is also significant damage to the endothelial and smooth muscle cells and obviously a predominance of glomerular damage in AKI due to glomerulonephritis [20, 21]. Studies have demonstrated that podocyte injury precedes tubular injury and can be seen as early as 30 min post-reperfusion in KIR injury in mice [22]. After the initial injury, surviving cells undergo a process of dedifferentiation and proliferation to replace damaged cells and restore integrity [23–25]. Previous studies have indicated that the kidneys are able to intrinsically regenerate after an episode of AKI provided that the threshold of damage is not too high [26, 27].

However, kidneys are unable to generate new nephrons, and maladaptive or repeated episodes of AKI will lead to further nephron loss and injury that is ultimately associated with CKD and end-stage renal disease (ESRD) [26–28]. In addition, a single episode of AKI puts patients at risk of future episodes of AKI, which, in combination with individual modifiers, increases the risk of developing CKD and ESRD [29, 30] (Figure 2). The AKI to CKD transition is a complex process that was reviewed recently by Sato and Yanagita [31]. The transition is mainly facilitated by maladaptive repair that facilitates fibrosis and CKD [32]: the

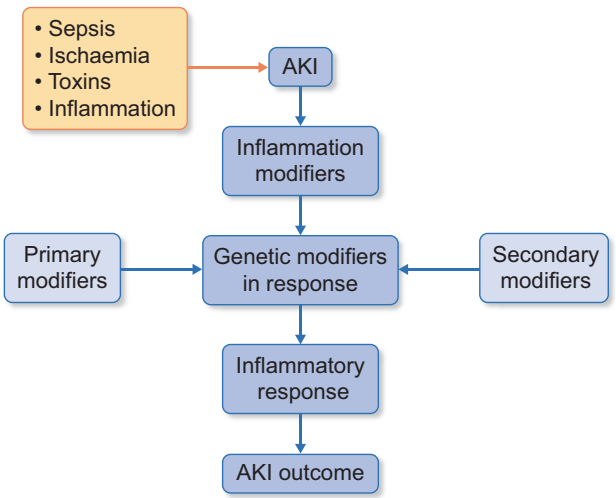

FIGURE 2: A summary of the pathway determining an individual patient's outcome of AKI. A patient experiences an episode of AKI following a certain stimuli, such as sepsis or ischaemia, resulting in an inflammatory process that can be modified by an individual's genetic predisposition and may be further insulted by primary modifiers including age and pre-existing disease. Secondary modifiers include additional hits such as haemodynamic instability, nephrotoxic pharmacotherapy or other interventions (radiological investigations). These impact on the subsequent inflammatory response and the eventual AKI outcome.

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process of dedifferentiation can lead to failed tubule recovery, a decrease in epithelial markers and an increase in mesenchymal markers [25, 33, 34]. Damaged tubules, as well as immune cell–derived myofibroblasts, are a source of pro-fibrotic factors and are associated with the subsequent development of fibrosis and scarring. Whereas the process of fibrosis is meant to prevent further damage, it also reduces renal function by promoting capillary rarefaction and exacerbating hypoxia and atrophia [32, 34, 35]. Currently >100 therapies have proven effective in animal models of AKI and yet none are effective in preventing AKI in people or preventing the transition from AKI to CKD [36]. Understanding the complex interaction between renal inflammation and injury may allow earlier identification and subsequent intervention to prevent the onset of irreversible fibrosis.

CLINICAL EXAMPLES OF AKI AND ITS INFLAMMATORY MECHANISMS

One must consider the clinical context in which kidney injury or inflammation has occurred: in several cases, the injury and/or inflammation may be sequelae of ongoing systematic disease or even due to genetic disorders or acquired injuries where inflammation may not classically be considered. Below we outline some clinical examples that either directly or indirectly affect kidney function and explore what factors may limit treatment options.

AKI following cardiac bypass surgery

The process of cardiopulmonary bypass is acknowledged to cause sudden alterations in renal perfusion, with consequent ischaemia and reperfusion cycles [37]. During ischaemia, aerobic respiration within mitochondria ceases. The metabolites of the citric acid cycle, required for aerobic respiration via electron transport, become depleted, except for succinate, which accumulates during ischaemia [38]. Upon reperfusion the accumulated succinate in mitochondria is rapidly oxidized, driving superoxide formation via reverse electron transport at complex I of the electron transport chain [38]. This burst of superoxide [39, 40] is then followed by further superoxide formation via the xanthine oxidase pathway and nicotinamide adenine dinucleotie phosphate oxidases [41]. Production of reactive oxygen species (ROS) activates a variety of pathways that lead to tissue injury. These include opening of the mitochondrial permeability transition pore, leading to apoptosis or necrosis, and induction of damage-associated molecular patterns, leading to activation of both innate and adaptive immune responses [42]. Production of ROS also induces pro-inflammatory transcription factors such as nuclear factor κB [43], leading to recruitment of inflammatory cells to the renal parenchyma and the potential for fibrosis [44]. Clinically between 30 and 50% of patients develop AKI following cardiopulmonary bypass surgery [45] and strategies to ameliorate this in adults have included large randomized controlled trials to evaluate the use of perioperative methylprednisolone, but with little benefit [46]. Typically patients have a period of AKI spanning several days while the repair mechanisms restore renal function. Of those with AKI, many (~12% in congenital heart disease) will develop CKD within 5 years [45].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease has traditionally been considered a disease of adulthood, however, chronic inflammation is observed early in this disorder, with M1 and M2 macrophages modulating fibrosis and increasing deposition of extracellular matrix to which inflammatory cells are recruited [47]. In mouse models, ablation of the adhesion molecule β_1 integrin reduces both the formation of cysts and fibrosis [48], suggesting that crosstalk between extracellular matrix and inflammatory cytokines may be a fruitful approach to disease management. Likewise, the physical presence of cysts in these patients makes controlling infection and inflammation difficult: antibiotics have some difficulty in penetrating infected kidney cysts, which makes urinary tract infections more damaging [49]. A recent development in this condition has seen the introduction of an effective pharmacological treatment to suppress the growth of kidney cysts using the vasopressin inhibitor tolvaptan [50] and preclinical studies are evaluating adenosine monophosphate–activated protein kinase as a signalling target [51].

Lowe syndrome/Dent2 disease

These are rare multisystemic X-linked disorders affecting brain, kidney, eyes and bone. The kidney disorder manifests in defective resorption of metabolites in the proximal tubule, leading, if untreated, to rickets, aminoaciduria and disturbance of parathyroid hormone signalling [52]. Treatments are lifelong supplementation of metabolites and close management of symptoms. These patients frequently develop kidney stones due to excessive calcium loss [52], which then deposits in the kidney, causing a progressive process of kidney scarring and fibrosis leading to ESRD between the second and fourth decades of life. Work in model systems suggests that defects in the causative gene OCRLinositol polyphosphate-5-phosphatase (*OCRL*) also manifest as increased amplification of inflammatory immune signalling [53]. Interestingly, Lowe syndrome patients frequently exhibit tenosynovitis, joint swelling and arthritis [54], which may indicate immune misregulation. This has been reversed in animal models by injection of virally encoded *OCRL* to affected chondrocytes [55], although this is not yet a therapy that can be deployed in humans.

FUTURE DIRECTIONS

Earlier detection using biomarkers

Standard clinical practice continues to focus on changes in serum creatinine and urine output as markers of kidney injury despite research on novel biomarkers receiving increased attention over the last 15 years [56]. The ongoing success of creatinine as the biomarker of choice is derived from the fact that it is endogenous, easily measured, well-validated and used in formal staging criteria. Creatinine's limitations are the relative requirement to have a comparative baseline value to aid interpretation, non-glomerular elimination via the proximal tubule and gastrointestinal tract and interference from commonly prescribed drugs [57]. A number of exogenous markers can be measured in the blood, urine and via nuclear imaging [58]. The use of exogenous markers of injury and function is much less frequently favoured due to the added technical complexity and additional expense. However, markers such as technetium-99m diethylenetriaminepentaacetate give useful additional information about the, for example, differential function between kidneys (split function).

Current clinical practice to measure renal inflammation remains limited. Renal histology remains the gold standard and

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is usually required in the diagnosis of acute glomerulonephritis [59]. However, interobserver variability can be poor, as demonstrated in a study assessing renal histology slides from patients with lupus nephritis [60]. Examining the urine for sediment and casts seems to have fallen out of favour, but in trained hands it can provide a wealth of information [61]. Glomerular inflammation may be inferred from the degree of proteinuria and serological markers such as C-reactive protein, erythrocyte sedimentation rate and eosinophilia may be suggestive of inflammatory conditions but are not renal specific.

Novel markers can be categorized as endogenous or exogenous. They can be measured in the serum, urine or via imaging methods. A list of considered biomarkers for AKI is presented in Table 1. Criticisms of these markers include the limited clinical settings that these are tested in, their role when measured in isolation, as recent studies have suggested the need to develop an AKI panel to compensate for specificity and sensitivity deficiencies, and that some markers may be generated extrarenally (e.g. neutrophil gelatinase-associated lipocalin in states of infection or physiological stress [62, 75]). In a clinical setting, an endogenous marker would be preferable to simplify the technical process in large patient groups. Due to its obvious proximity, urine has been implicated as the best site for early detection of kidney injury [75], but despite many of these novel biomarkers appearing within the literature, none of these are in routine clinical use.

Table 1. A summary of the urine biomarkers implicated in renal injury and inflammation

Biomarkers implicated in renal injury [61–71]	Biomarkers implicated in renal inflammation [72–74]
Neutrophil gelatinase-associated lipocalin	Pentraxins
Kidney injury molecule-1	IL-1-β
Cystatin C	Tumour necrosis factor-α
IL-6 and -18	IL-8
Retinol-binding protein	IL-18
Glutathione S-transferase (α, η, π)	IL-12
Urinary insulin-like growth factor-binding protein 7	Interferon γ
Tissue inhibitor of metalloproteinases-2	Anti-inflammatory cytokines
Micro-ribonucleic acids	IL-1 receptor antagonist
Na^+/H^+ exchanger isoform 3	IL-4
Perforin	TGF-β
Granzyme B	Adipokines and related compounds
Monocyte chemoattractant protein-1 (chemokine ligand 2)	Visfatin
N-acetyl-β-D-glucosaminidase	Resistin
Liver-type fatty acid-binding protein	Leptin
Netrin-1	CD163
Clusterin	Vascular cell adhesion molecule-1
β2-microglobulin	E-selectin
Matrix metalloproteinases	Neopterin (monocyte/macrophage activator)
Endogenous ouabain	
Selenium-binding protein 1	
BPI fold containing family A member 2 salivary protein	
Chromophores via multispectral optoacoustic tomography, e.g. IRDye 800CW carboxylate	
Fluorophores via transcutaneous detection, e.g. fluorescein isothiocyanate–sinistrin	
Dickkopf-3	

Many urinary biomarkers have been evaluated to determine their role in the early identification of renal injury and inflammation within the literature, as demonstrated within this table. While many are implicated in isolation, their strength is evident once combined to produce a panel of biomarkers.

Targets to modify AKI outcome

Treatment options in AKI remain experimental and, aside from treating the underlying cause, current clinical management for AKI is conservative, with careful fluid and electrolyte control and supportive renal replacement therapy when indicated. Virtually all immune cells are implicated in the pathogenesis of AKI and blockade of several innate immune receptors (e.g. toll-like receptor 2) has been shown to ameliorate experimental AKI in animal models, although their translation into clinical practice is uncertain [36]. Targeting pro-fibrotic signalling cascades may be another useful way to modify AKI, for example, fibroblast growth factor 23 (FGF23) induces pro-fibrotic signalling via activation of the transforming growth factor (TGF)-β pathway in kidney cells primed with injury. Individual genetic variants may predispose patients to increased concentrations of FGF23 and modify the inflammatory response to acute injury stimuli [76]. Direct inhibitors specifically targeting FGF23 are not available. However, it may be indirectly reduced by inhibition of the renin–angiotensin–aldosterone system. Post-translational modification proteins called small ubiquitin-related modifiers are extensively expressed in eukaryotes and influence the individual response to the activation of the nuclear factor κB inflammatory signalling pathway. Therefore they play a central regulatory role in the inflammatory response and may have a role in contributing to the TGF-β/Smad pathway, leading to fibrosis of the kidney [77].

Preclinical modelling of AKI

Part of the reason for the limited treatment options is the inability of existing preclinical disease models to accurately recapitulate kidney injury. Additionally, the lack of validated AKI biomarkers has resulted in a disconnect and ultimately poor translation between preclinical and clinical models [78]. Inflammation and kidney injury are tightly coupled and for a model to be useful for the study of mechanisms or to assist with drug discovery, it needs to incorporate this cyclical phenomenon. However, modelling of this complexity is difficult, with researchers subsequently forced to strike a balance between the scalability of an experimental model and the degree of disease homology (Figure 3).

The approach with the greatest scalability is *in silico* modelling, which uses bioinformatics and chemoinformatics to hypothesize and test during drug discovery [79]. These methods are capable of screening virtual compound libraries and simulating their binding using structural data. However, computational approaches are limited by our understanding of the binding targets in question [80] and are held back by biomarker discrepancies [78]. In addition, *in silico* models are often validated using poor *in vitro* models, thus reducing disease

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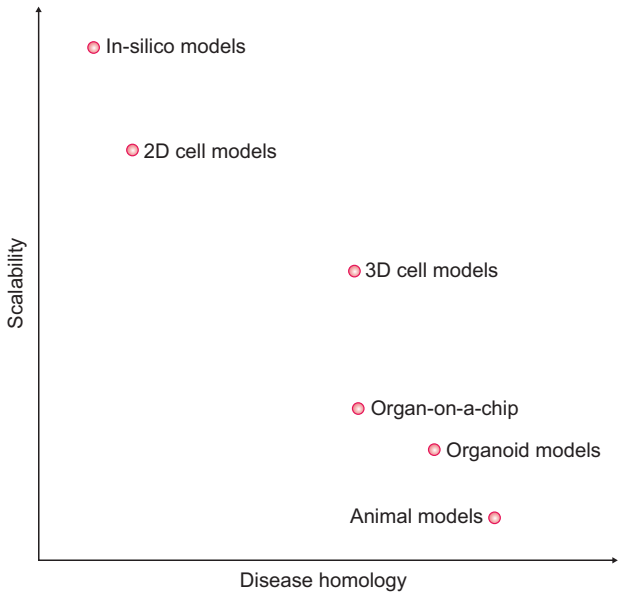

FIGURE 3: Experimental models to evaluate therapeutic options in AKI. Experimental models to evaluate kidney disease suffer from the balance of reflecting accurate disease homology versus their ability to be upscaled in order to mass evaluate potential benefits of novel pharmacological treatments. As shown, animal models often reflect the disease best, but lack scalability to evaluate drugs on a large-scale basis, whereas *in silico* models provide a platform suitable for testing many treatments at the cost of reduced disease homology. In practice, a balance between scalability and disease homology is required prior to early phase clinical trials in humans.

homology. Two-dimensional cell models are also highly scalable and conditionally immortalized human podocytes [81], glomerular endothelial cells [82] and mesangial cells [83] are used routinely to model kidney disease *in vitro*. For high-throughput assays, cells are often grown in monoculture on culture plastic in a way far removed from their *in vivo* niche. For podocytes, this has been shown to deleteriously affect proteome and transcriptome readouts, hampering their capacity for simulating disease [84].

It is apparent that co-culturing renal cells in three dimensions helps to better recapitulate the three-dimensional architecture and signalling environment of *in vivo* tissue [85, 86]. Moreover, these bioengineered models of acute and chronic injury offer superior toxicology sensitivity than their two-dimensional cultured counterparts [87]. However, models such as this are far less scalable and reproducible than two-dimensional cell models and as such are not suitable for high-throughput screening. Kidney-on-a-chip approaches seek to add flow to cultured cells and have successfully bioengineered a kidney tubule from conditionally immortalized human proximal tubule epithelial cells [88]. It is also possible for multiorgan systems to be established, including sequentially connected gut, liver and kidney cells [89]. These models have the potential to simulate the cyclical nature of kidney injury, although they are currently very low throughput, impeding their usefulness for screening.

The advent of kidney organoids from induced pluripotent stem cells represents a significant step in the right direction for improving disease homology of *in vitro* models [90]. These systems have the potential to model genetically acquired disease such as Alport syndrome [91]. Improving the scalability of these models is once again a challenge, however, if they are to be used for drug screening. *In vivo* animal disease models (despite modelling non-human disease) currently offer the greatest simulation of the many comorbidities that underpin kidney injury. Among these, rodent models of ischaemia-reperfusion [92] and uretic obstruction [93] are most ubiquitous. However, it is not possible to use animal models for the early stages of compound screening, which means that cell models must first be used.

There is a clear need for refinement in the high-throughput models used in the early stages of drug discovery. An *in vitro* model of kidney injury that is jointly scalable and representative of the disease, with transferable biomarker readouts, would drastically improve the translation between preclinical and clinical models.

CONCLUSIONS

Historically the lack of consensus definitions for AKI and a limited understanding of the pathophysiology of AKI has impeded advances in the management of these patients and the development of new treatments. The advent of a widely accepted definition of AKI has opened the way for more valuable research in this field. Here we have considered the role of inflammation within the mechanism of kidney injury and identified future directions for research that will translate into improved understanding of mechanisms to benefit patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

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